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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,973	03/01/2002	Kesavan Esuvaranathan	488002000200	6742

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,973	ESUVARANATHAN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-16,18-31,33,34,36-41,43,44,46-57 and 59-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,3-16,18-31,33,34,36-40,57 and 59-65* is/are allowed.

6)☒ Claim(s) *41,43,44 and 46-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's petition under 37 CFR 1.78(a)(3), filed 3/7/06, was granted on 8/10/06. The priority claims to PCT/SG00/00130, filed 9/1/2000 under 35 USC 120 or 365(c), and to Australian Application PQ2593/99, filed 9/1/1999.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/7/06 has been entered.

Claims 1, 3-16, 18-31, 33, 34, 36-41, 43, 44, 46-57, and 59-65 remain pending in the application.

Claims 57 and 59-65 are directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(B), claims 1, 3-16, 18-31, 33, 34, 36-41, 43, 44, and 46-56, directed to the process of making or using an allowable product, previously withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Because all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, **the restriction requirement as set forth in the Office action mailed on 10/7/04 is hereby withdrawn**. In view of the withdrawal of the restriction

requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Specification

Applicant's amendment filed 3/7/06 overcame the objection to the specification under 35 U.S.C. 132(a) for introduction of new matter.

Drawings

Fig. 8B is objected to because, although the brief description of the drawing refers to "Figures 8Bi-iv", and descirbes 'i', 'ii', 'iii', and 'iv', there are no such labels in Fig. 8B.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41, 43, 44, and 46-56 are rejected under 35 U.S.C. 112, first paragraph,

because the specification, while being enabling for methods of treating a superficial bladder tumor in the mucosal layer of the lumenal surface of a bladder by contacting the lumenal surface of the bladder with a transfection composition comprising (i) a polynucleotide; (ii) a cationic lipid, a cationic polymer or a dendrimer, or combinations thereof; and (iii) a solubilized cholesterol preparation, wherein the polynucleotide is capable of expressing a protein selected from the group consisting of interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-18 (IL-18), interferon-alpha, interferon-beta, interferon-gamma, granulocyte-macrophage colony stimulating factor (GMCSF), granulocyte colony stimulating factor (GCSF), p53, and an antagonist of vascular endothelial cell growth factor (VEGF), does not reasonably provide enablement for methods of treating bladder cancer in the muscular layer of the bladder, or for methods of treating superficial bladder cancer with nucleic acids encoding interleukin-6 (IL-6), interleukin-9 (IL-9), interleukin-11 (IL-11), macrophage colony stimulating factor (MCSF), heat shock protein (HSP), a tissue inhibitor of metalloproteinases (TIMP), or a fibronectin receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 41, 43, 44, and 46-56 are directed to methods of treating cancer of the bladder by intravesical administration of a composition comprising i) a polynucleotide that imparts anticancer activity against bladder cancer cells, ii) a cationic lipid, a cationic polymer or a dendrimer, or combinations thereof; and (iii) a solubilized cholesterol preparation, wherein the solubilized cholesterol preparation comprises cholesterol

solubilized with a cyclodextrin.

The claims embrace any type of bladder cancer including superficial tumors and tumors of the muscular layer of the bladder.

Sutton (Mol. Ther. 2(3): 211-217, 2000) taught that administration of adenoviral vectors to the lumenal surface of the bladder resulted in transduction of only the most superficial layers of the bladder mucosa, and did not result in penetration to an intramuscular tumor. See abstract, and paragraph bridging columns 1 and 2 on page 214.

The instant specification showed that intravesical administration of cyclodextrin-solubilized cholesterol and nucleic acids resulted in transfection of the lumenal bladder epithelium. See Figs. 6 and 10, and specification at page 33, lines 1-6, and page 33, line 21 to page 34, line 2.

Neither the prior art of record nor the specification provide evidence that nucleic acid or viral vectors can be delivered to cells beneath the lumenal bladder epithelium, such as smooth muscle cells, by intravesical administration.

The specification provided no guidance as to how to obtain transfection of tumors located beneath the lumenal bladder epithelium, e.g. in the muscle of the bladder, by contacting the lumenal surface of the bladder by intravesical administration.

In view of the state of the art regarding penetration of the nucleic acid vectors beyond the lumenal bladder epithelium, e.g. to the muscular layer of the bladder after intravesical administration, the inability to treat invasive tumors by intravesical administration of nucleic acids, the lack of a working example of such treatment in the

specification, and a lack of guidance as to how to obtain transfection of cells beyond the epithelial layer by intravesical administration, one would have had to perform undue experimentation in order to practice the claimed method commensurate in scope with the claims, e.g. to treat tumors of the muscular layer of the bladder by administration of polynucleotides to the lumenal surface of the bladder by intravesical administration.

Regarding the list of proteins recited in claim 50, the specification is considered to be enabling for interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-18 (IL-18), interferon-alpha, interferon-beta, interferon-gamma, granulocyte-macrophage colony stimulating factor (GMCSF), granulocyte colony stimulating factor (GCSF), p53, and an antagonist of vascular endothelial cell growth factor (VEGF), but not for interleukin-6 (IL-6), interleukin-9 (IL-9), interleukin-11 (IL-11), macrophage colony stimulating factor (MCSF), heat shock protein (HSP), a tissue inhibitor of metalloproteinases (TIMP), or a fibronectin receptor.

A search of the prior art provided support for the use of interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-18 (IL-18), interferon-alpha, interferon-beta, interferon-gamma, granulocyte-macrophage colony stimulating factor (GMCSF), granulocyte colony stimulating factor (GCSF), p53, and an antagonist of vascular endothelial cell growth factor (VEGF) in the treatment of bladder cancer. However, the prior art did not support the use of interleukin-6 (IL-6), interleukin-9 (IL-9), interleukin-11 (IL-11), macrophage colony stimulating factor (MCSF), heat shock protein (HSP), a tissue inhibitor of metalloproteinases (TIMP), or a fibronectin receptor for this purpose. For example:

Cardillo et al (Anticancer Res. 20(6B): 4579-4583, 2000) taught that HSP-90 and IL-6 expression correlated positively with high grade and muscle invasive tumors. (see abstract).

Medline Accession No 2004528586 (2004) taught that antisense oligonucleotides directed against HSP 70 enhanced the sensitivity of bladder cancer cell lines to mitomycin, suggesting an inverse correlation between HSP 70 and effectiveness of an anticancer drug. See abstract.

Syrigos et al (Urology 61(3): 677-680, 2003) taught that HSP 70 is frequently overexpressed by bladder cancer cells, suggesting to one of skill in the art that delivery of HSPs to bladder cancer cells would not be therapeutic. See abstract.

Grignon et al (Cancer Res. 56(7): 1654-1659, 1996) taught that TIMP expression is positively associated with tumor invasion and metastasis in many human cancers, and are associated with poor outcome in invasive bladder cancer. See abstract.

Medline Accession No. 2002430653 taught that fibronectin receptors mediated activation of tumor cells, leading one of skill in the art to doubt its effectiveness as an antitumor drug.

A search of the prior art revealed no evidence that it was routine in the art to use interleukin-9 (IL-9), interleukin-11 (IL-11), or macrophage colony stimulating factor (MCSF), in the treatment of bladder cancer. As the physiological art is considered to be unpredictable (MPEP 2164.03), the simple statement that these proteins are useful to treat bladder cancer is not considered to be enabling in the absence of some explanation of why they should be useful, particularly in view of the state of the art.

In view of the state and unpredictability of the art as discussed above, the absence of any relevant working example, and the absence of relevant guidance in the specification, one of skill in the art would have to perform undue experimentation in order to practice the invention commensurate in scope with the claims.

Conclusion

Claims 1, 3-16, 18-31, 33, 34, 36-40, 57, and 59-65 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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